

Interoception and Inflammation in Psychiatric Disorders

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ABSTRACT

Despite a historical focus on neurally-mediated interoceptive signaling mechanisms, humoral (and even cellular) signals also play an important role in communicating bodily physiological state to the brain. These signaling pathways can perturb neuronal structure, chemistry and function leading to discrete changes in behavior. They are also increasingly implicated in the pathophysiology of psychiatric disorders. The importance of these humoral signaling pathways is perhaps most powerfully illustrated in the context of infection and inflammation. Here we provide an overview of how immune activation of neural and humoral interoceptive mechanisms interact to mediate discrete changes in brain and behavior and highlight how activation of these pathways at specific points in neural development may predispose to psychiatric disorder. As our mechanistic understanding of these interoceptive pathways continues to emerge it is revealing novel therapeutic targets, potentially heralding an exciting new era of immunotherapies in psychiatry.

INTRODUCTION

Inflammation is increasingly implicated in the pathogenesis of many common psychiatric disorders. Similar to other physiological processes, interoceptive pathways play a critical role in communicating immune state to the brain. Within the body, the immune system acts as a distributed chemosensory system using diverse pattern-recognition receptors (PRRs) to detect the presence of pathogen- (PAMP) and tissue stress or damage- (DAMP) associated molecular patterns. On activation, immune cells release immune and inflammatory mediators, notably cytokines. Parallel neural, humoral and cellular interoceptive pathways then communicate these changes in immune state to the brain to trigger alterations in mood and cognition, motivation, and neurovegetative processes (1-3). However, immune activity is not solely regulated in the periphery. Top-down influences from the brain can dampen peripheral inflammation via hypothalamic release of CRH (corticotrophin-releasing hormone) and the vagus nerve inflammatory reflex (4). Conversely, sympathetic projections to lymphoid tissue, including the bone marrow, lymph nodes, and spleen can prime immune responses to actual or perceived environmental threats (5-7).

Typically, inflammation is short-lived and these adaptive changes in behavior that serve to reprioritize behavioral responses towards the insult rapidly return to baseline (8). However, when inflammation is severe, becomes chronic (9), or occurs during critical developmental windows (10) or on a background of neurodegeneration (11) or chronic severe stress, prolonged activation of interoceptive pathways and consequent neurochemical changes can precipitate long-standing maladaptive neurobiological and behavioral changes that are implicated in the pathophysiology of many common psychiatric disorders.

Recent progress in understanding the molecular and cellular processes underlying bidirectional immune-brain interactions is revealing the complex nature of interoceptive signaling of immunity. For example, it is now recognized that during periods of severe stress

increased sympathetic outflow can result in sustained splenic enlargement and production of monocytes with enhanced migratory and pro-inflammatory phenotypes in rodents (7, 12). Historically, only the adaptive immune system has been considered capable of retaining a 'memory' of past events. However, these persistent immunological changes appear to provide a peripheral, bodily index of prior stress exposure that accords with recent recognition of wider innate immune system memory (13). Supporting this, subsequent stress exposure (even when sub-threshold) results in significant trafficking of these 'pro-inflammatory' monocytes to the brain where they then differentiate into tissue macrophages to promote inflammatory signaling and amplify behavioral stress responses (7). Findings such as this are highlighting the importance of cellular, as well as more conventional humoral and neural pathways and underscore the need to broaden our conceptualization of interoceptive signaling. As we discuss below, these developments are also beginning to reveal novel therapeutic drug targets and allow a reappraisal of how some established therapies might be exerting therapeutic efficacy.

HOW IS INFLAMMATION COMMUNICATED TO THE BRAIN?

Visceral afferents: Similar to the signaling of other physiological processes, central communication of peripheral inflammation appears dependent on interoceptive visceral afferents travelling in the vagus and other autonomic nerves (14). These afferents express cytokine-binding sites (15). Antigen presenting cells accumulate around site/s of inflammation then signal to visceral afferents using cytokine-dependent (16) and independent mechanisms (17). Signaling via this neural interoceptive pathway is rapid, inducing c-Fos expression in the solitary nucleus (NTS) (the primary projection nucleus of the vagus) and higher projection regions within an hour of challenge in rats (14). Human functional imaging studies demonstrate activation of a similar neurally-mediated

interoceptive pathway (projecting to ventromedial posterior thalamus and then mid/posterior insula) within 2-3 hours of inflammatory challenge (18-20) (Figure 1). Projections from the NTS to the vagal dorsal motor nucleus and nucleus ambiguus initiate reflex responses including the inflammatory reflex, which regulate the magnitude of innate immune responses (4). Conversely, projections to the caudo- and then rostro-ventrolateral medulla influence sympathetic outflow. Ascending projections to the hypothalamus, hippocampus, extended amygdala, striatum, cingulate, insula and higher cortical areas underpin discrete changes in behavior (17, 21) (See Figure 2 for 'circuit' diagram). Though beyond the scope of the current review, a number of recent approaches have applied principles of hierarchical predictive coding and/or Bayesian active inference to information processing within these regions to provide a theoretical framework linking them to discrete changes in behavior and/or psychopathological features (22-24)

Humoral pathways: Circulating inflammatory mediators also activate humoral interoceptive pathways. Some mediators can access the brain directly via the sensory circumventricular organs located in the walls of the third and fourth ventricles (25). In these regions loops of fenestrated capillaries surrounded by large perivascular spaces facilitate a dramatic increase in surface area and permeability (26). This, together with dense receptor expression, enables detection of large circulating molecules including those that provide information about systemic inflammation. While the circumventricular organs are specialized for the detection of low concentrations of circulating factors, some inflammatory mediators e.g. interleukin (IL)-6, interferon (IFN)- α and immune cells (e.g. stress-induced monocytes) can also enter the central nervous system (CNS) in small quantities in other regions to exert direct functional effects (7, 27). Perhaps the best illustration of humoral interoception is inflammation-induced pyrexia. Here, cytokines (particularly IL-6) act directly on the brain endothelium to trigger prostaglandin E2 release which acts as a pyrogen at the hypothalamic median preoptic nucleus (28).

Cellular pathways: Monocytes and Microglia: As highlighted earlier, direct monocyte trafficking also provides a cellular interoceptive pathway for communicating immune state to the brain (7). Though typically low during health, monocyte trafficking increases significantly following severe stress in rodents, and appears to serve as a mechanism for amplifying behavioral stress responses given a history of previous sustained threat (7). Transduction of interoceptive signaling of inflammation also involves microglia (specialized brain macrophages with distinct phylogenetic origins) (29). In health, microglia show highly dynamic behavior, expanding and retracting branched ramifications to continuously sample neighboring cells and extracellular space (30). In this 'resting' state they are implicated in synaptic pruning (31), a process critical for neural plasticity and learning. Like peripheral macrophages, microglia exist in multiple 'activated' forms associated with distinct changes in morphology and secretory profile that can alter local neuronal and endothelial function (32). Within the brain, activation of microglia occurs in response to diverse danger-associated homeostatic changes e.g. ischemia. However, it is also observed following exposure to repeated environmental stresses, which is likely mediated via activity-dependent release of ATP in response to neuronal glutamate signaling (33).

Important to their role in interoceptive signaling, microglia are also sensitive to systemic danger signals including peripheral inflammation. In this context, microglial activation likely occurs through activation of interoceptive pathways that involve passage of cytokines across the BBB (34), release of prostaglandin E2 by perivascular and endothelial cells in response to intravascular inflammation (35) or entry of stress-sensitive monocytes into the CNS (33). In rodents, peripheral inflammation results in rapid activation of microglia within the circumventricular organs, leptomeninges, and choroid plexus, which release tumor necrosis factor (TNF) to trigger a cascade of microglial activation that spreads across the brain (36). Translocator protein (TSPO) PET (a marker of activated microglia) has illustrated a similar

pattern of widespread microglial activation following LPS-induced peripheral inflammation in humans (37).

Below, we describe how signaling via these pathways can result in regional disturbances in neuronal metabolism, neurotransmitter release and brain activity associated with discrete features of psychopathology.

INTEROCEPTIVE SIGNALING OF INFLAMMATION IN PSYCHIATRIC DISORDERS

MOOD DISORDERS

Arguably the strongest evidence implicating interoceptive signaling of inflammation to psychiatric illness is for mood disorders. Stress, particularly in early life, is a major vulnerability factor for mood disorders and has been linked to sustained inflammation in human meta-analysis (38). Preclinical studies link this stress vulnerability to bi-directional interactions between the brain and immune system. Specifically, repeat exposure to severe social stress (using the repeated social defeat (RSD) model) activates fear-associated neural circuitry. It also increases sympathetic outflow which acts on the bone marrow and spleen to bias myeloid precursor cells (particularly monocytes) toward a glucocorticoid resistant and primed lineage (33). Sustained glutamatergic activity within brain regions mediating fear responses also triggers local microglial priming, likely through activity-dependent ATP release from astrocytes binding to microglial P2X7 receptors (7).

Interoceptive pathways link these central and peripheral immune changes and make a powerful contribution to the cumulative effects of repeated stress. For example, in addition to release of inflammatory mediators including IL-1 (which modify neuronal function and disrupt monoamine synthesis) (33, 39), activated microglia also release chemokines (e.g. CCL2 and CX3CL1), which trigger homing of monocytes primed by previous stress exposure

from the circulation into stress-associated brain regions (33). Pro-inflammatory cytokine release from primed monocytes that have entered the CNS then further contribute to the maladaptive effects of chronic stress. This cellular interoceptive signaling pathway also appears to underlie the process of 'stress-sensitization' whereby previously stressed animals show a heightened propensity to maladaptive stress responses to later sub-threshold stressors (12, 40) (Figure 3).

Interoceptive signaling of inflammation also plays a role in human depression. Cumulative meta-analyses now provide convincing evidence for raised peripheral inflammatory markers particularly IL-6 and CRP in a subset of depressed patients (41). Gene expression analyses also implicate IL-6, TNF and interferon-alpha (IFN- α) signaling pathways (42-44). This increase in peripheral inflammatory markers is linked to disturbances in brain function. For example, depressed patients with raised CRP show impairments in the functional connectivity of ventral striatum and medial prefrontal reward and motivation processing areas (39). Recently, depression has also been linked to CNS inflammation, with widespread increases in activated microglia observed using TSPO PET (45). Perhaps the most powerful evidence supporting an etiological role for inflammation comes from patients receiving prolonged IFN- α therapy, up to 50% of whom develop major depressive episodes (46, 47).

Here, IFN- α appears to trigger depression-associated behavioral changes through activation of humoral and, to a lesser extent, neural interoceptive pathways (48). In humans, therapeutically administered IFN- α is observed in the CSF (49). In rodents, peripheral IFN- α rapidly up-regulates interferon-sensitive gene expression within predominantly sub-cortical structures (50, 51). Together, these studies support rapid activation of humoral interoceptive signaling pathways. Within the brain parenchyma, IFN- α shows a marked predilection for subcortical structures including the basal ganglia and hippocampus (51, 52). This is reflected in imaging studies of patients receiving IFN- α for the treatment of hepatitis-

C who show changes in striatal glucose metabolism, dopamine uptake, glutamate (53, 54) and microstructural changes in striatal water distribution (48, 55). The functional significance of these striatal changes is supported by significant correlations with IFN- α -induced changes in motivation and/or fatigue (53, 54).

Pro-inflammatory cytokines also increase expression of the enzyme indoleamine 2,3-dioxygenase (IDO) shunting tryptophan metabolism away from serotonin synthesis into the kynurenine pathway. This results in the production of a number of neuroactive metabolites including the neuroprotective NMDA receptor antagonist, kynurenic acid (KynA) as well as the potentially neurotoxic NMDA receptor agonists, 3-hydroxykynurenine (3HK) and quinolinic acid (QA) both of which can influence glutamatergic signaling. During IFN- α treatment, CSF concentrations of each of these metabolites increases, with increases in KynA and QA correlating with depressive symptoms (56). Under inflammatory conditions, brain production of QA tends to overshadow that of KynA (57) such that the ratios KynA/3HK and KynA/QA can provide a sensitive index of the competing effects of these neuroactive metabolites. Several investigators have now reported reduced KynA/QA in major depressive disorder (MDD) as well as bipolar and schizoaffective disorder, which is additionally linked to altered hippocampal and medial prefrontal cortex volume/ function (58-61). These studies illustrate putative mechanisms through which activation of interoceptive signaling pathways can lead to neurochemical change and shifts in behavior.

SCHIZOPHRENIA AND AUTISM SPECTRUM DISORDER

Like mood disorders, schizophrenia and autism spectrum disorders (ASD) have been associated with raised circulating pro-inflammatory cytokines in cohort studies (62). However, unlike depression, emerging evidence suggests that this pro-inflammatory phenotype may have its origins in early development. Epidemiological work has long

identified in-utero infection as a risk factor for development of schizophrenia in offspring (63). Maternal exposure to infection has also been linked with autism, with a recent prospective study reporting a dosage effect such that three or more episodes of fever during the second trimester raised the risk of having a child with ASD threefold (64).

Preclinical studies of maternal immune activation, (typically modeled with the viral mimetic polyinosinic:polycytidylic acid (poly I:C)), lend support to epidemiological studies by showing sustained abnormalities in rodent analogues of the repetitive movements and deficits in social behavior, sensory gating and cognition that characterize autism and/or schizophrenia (65). Post-mortem and animal imaging studies further show that maternal immune activation leads to changes in synaptic connectivity and neuroplasticity that may manifest as changes in cortical thickness and brain volume (65). The mechanisms underpinning this dysregulation of neural development remain to be fully characterized, though suggest that even before birth interoceptive-signaling pathways may play a role in human psychopathology.

Since most pathogens do not directly infect the fetus, early infection is thought to impair normal brain development via activation of the maternal immune system. Preclinical models indicate that maternal cytokines are necessary for development of disease in offspring, though whether cytokines cross the placenta or act indirectly remains unclear (65). Either way, maternal immune activation appears to initiate changes in gene expression that affect neuronal migration, synaptic pruning, and myelination. Here again microglia may play a role since these cells are involved in multiple aspects of brain development, especially synaptic pruning (66). Fetal oligodendroglia may also be impacted: in a recent study, poly(I:C) administration resulted in down-regulation of genes involved in myelination in the medial PFC and nucleus accumbens that correlated with spatial memory deficits in the offspring. Further, the viral mimetic group had a greater myelin water fraction in the cortex (including

insula), hippocampus, and cerebellum, potentially indicating changes in the microstructure of the myelin sheath (67). Nonetheless, since most maternal infections do not directly lead to schizophrenia or ASD, subsequent “hits” taking the form of stress or adult-onset infections may be necessary for the manifestations of psychiatric disorders (65, 68).

Analogous to what is described in chronic stress, these second “hits” may dysregulate an already sensitized or ‘primed’ immune system leading to the neural and behavioral abnormalities characteristic of schizophrenia and ASD. A case in point is microglia which are known to be primed by infection (69), are increased in density in schizophrenia post-mortem (70), and show a shift towards a primed morphology in ASD (71).

LINKING INTEROCEPTION TO DISCRETE BEHAVIORAL PHENOTYPES

Most human studies addressing how interoceptive signaling of inflammation contributes to discrete dimensional psychiatric constructs have adopted an experimental medicine approach using a variety of inflammatory challenges. Some use vaccines (19) or inhaled antigens (72) to induce mild increases in inflammatory cytokines similar to those observed in depression; others low-dose lipopolysaccharide (LPS) to induce more robust pro-inflammatory responses (18, 73). Despite the variety of inflammation-induction techniques used, increases in insula activity are commonly observed, consistent with activation of a neurally mediated interoceptive pathway (Figure 1). Interestingly, many of these studies also link changes in insula activity to shifts in subjective experience (18-20), particularly fatigue, consistent with the proposed role of the insula in subjective experiential states (74).

MOTIVATION

During infection, interoceptive signaling of inflammation rapidly reorients motivation, impairing reward-related behavior and increasing sensitivity to punishments, particularly pain (8). This serves to prioritize whole organism responses towards fighting the infecting agent. However, if sustained may predispose to the development of MDD or chronic pain syndromes (25).

A wealth of studies has identified a critical role for the ventral striatum in mammalian reward processing and appetitive motivation (see (75) and citing articles). Within the midbrain, dopaminergic cells encode a reward prediction error, with their firing rate increasing (or decreasing) if rewards are higher (or lower) than predicted (76). Projections to the ventral striatum serve to update value estimates for available options and bias behavior to maximize long-term future reward. Recent studies have started to clarify how interoceptive signaling of inflammation can disrupt these processes. For example, peripheral inflammation results in an acute reduction in ventral striatal encoding of reward prediction error signal (77). It is also linked to disrupted presynaptic dopamine synthesis in humans (53) and reduced CSF concentrations of the dopamine metabolite homovanillic acid in monkeys (78). Cytokine associated reduction in dopamine synthesis may also be achieved by reducing CNS concentrations of tetrahydrobiopterin, an essential dopamine synthesis cofactor (79). Alternately, dopamine neurotransmission may be reduced by either activation of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) (leading to the formation of neurotoxic kynurenine metabolites) (25) or by increasing expression of reuptake transporters (79-82). Together, these implicate humoral interoceptive pathways in the reward-related motivational impairment characteristic of inflammation.

Though most studies of motivation have focused on reward, some brain areas implicated in neural interoceptive signaling (e.g. Insula) are also linked to choices associated with potential losses (21, 74, 83, 84). Specifically, anterior insula cortex appears to encode a

punishment prediction error signal linked to learning to avoid punishing outcomes (83). In patients with selective insula lesions this signal is disrupted and punishment sensitivity impaired (85). Conversely, during inflammation when interoceptive signaling is increased, insula encoding of punishment prediction error and sensitivity to punishments are enhanced (77). This suggests that relative sensitivity to reward and punishments can be dynamically modulated as a function of interoceptive signaling of inflammation, flexibly enhancing loss minimization during threats (like infection) but maximizing responses to gains during health. Though potentially beneficial during acute infections when substantial metabolic resources are diverted towards fighting infection, when inflammation is chronic this mechanism may underlie the maladaptive motivational changes observed in depression.

PSYCHOMOTOR RETARDATION

Psychomotor retardation is defined as a slowing-down of thought and physical movements. It is ubiquitous during infections (86, 87), and can be readily induced by even mild inflammatory challenges (88). It is also a cardinal symptom of depression (89) and a notable feature in a sub-set of patients with schizophrenia. In rodents, systemic inflammation consistently suppresses locomotor activity resulting in increased periods of immobility (90). IL-6 is strongly implicated in these motor-suppressing effects, which are reduced in IL-6 knockout mice (91) and following blockade of IL-6 signaling (92, 93).

In humans, low-level inflammation has been shown to selectively modulate substantia nigra reactivity during both low-level button press and more challenging color word Stroop tasks (88). Corroborating effects in rodents, this study also showed a tight correlation between induced changes in circulating IL-6 and motor response slowing across both congruent and incongruent Stroop trials suggesting an action on low-level pre-cognitive processes. Changes in IL-6 and left substantia nigra responses also predicted individual sensitivity to

inflammation-induced motor slowing. This association between IL-6 and poorer performance on simple and choice movement time tasks has subsequently been replicated in MDD patients (94).

This finding is noteworthy as the substantia nigra is the major source of dopamine within the brain. Projections to the striatum play a critical role in facilitating movement (95) and modulating motor responses to stimulus salience (96); they are also linked to inflammation-associated reductions in novelty salience (97). Lower striatal dopamine transporter activity is also linked to slower motor responses in the healthy elderly (98), and lower striatal presynaptic dopamine is reported in patients with depression and psychomotor retardation but not anxiety (99). Recently, psychomotor slowing in depression has also been linked to lower left basal ganglia glutamate (the other major neurochemical input to the striatum) and higher plasma and CSF C-reactive protein (CRP) (100).

Together, these studies support a central role for ascending dopaminergic (substantia nigra) and descending glutamatergic inputs into the dorsal striatum in psychomotor retardation associated with both inflammation and depression. During infection, slowing of psychomotor responses likely facilitates immune function by preserving energy and conserving heat. The convergence of findings across depression and inflammation suggests that chronic activation of these mechanisms may differentiate patients presenting with predominantly psychomotor or anxiety symptoms.

SLEEP

Pro-inflammatory cytokines (particularly IL-1 and TNF) are sleep regulatory agents that modulate slow wave sleep (101). During neuronal activity, co-release of ATP which acts on microglial P2X7 receptors to induce IL-1 and TNF release is believed to provide a potential

mechanism for enabling the brain to track prior usage history (102). During systemic inflammation, dynamic interactions between peripheral and central cytokines potentiate the effects of IL-1 and TNF on sleepiness, duration of non-REM sleep and slow wave power (102). Vagotomy attenuates some of these actions in rodents supporting a role for neural interoceptive pathways in mediating the effects of inflammation on non-REM sleep (103). Sleepiness and disrupted sleep are common features of many human inflammatory disorders (101) and are observed following acute inflammatory challenge (104) demonstrating the importance of interoceptive signaling in regulating sleep in response to systemic inflammation. Conversely, sleep also mediates susceptibility to infection during exposure to airborne respiratory viruses, further demonstrating the bidirectional nature of immune-brain communicatory pathways (105).

Sleep disturbance is also an important risk factor for depression (106-108) conceivably because it increases inflammation (109-111), which as discussed above, likely plays a causal role in some forms of psychiatric illness. Perhaps because the vagus nerve is involved in the processing of sleep signals (112), depressed subjects with sleep disturbance have interoceptive deficits such as reduced accuracy in their perception of their heart beats but increased subjective perception of interoceptive sensitivity (113). Conversely, high cardiac vagal control, as evidenced by high resting heart-rate variability, has been reported to be associated with better subjective and objective sleep quality in healthy women (114).

MEMORY

Microglia and inflammatory cytokines influence a number of processes critical to learning and memory including long-term potentiation (LTP), synaptic plasticity and neurogenesis. In health these immunological processes support the remodeling of neural circuits to promote learning and memory (3, 31). However, during systemic inflammation interoceptive signaling

can disrupt this positive regulatory function, impairing memory. Typically this memory impairment is mild and reversible (115), however when inflammation is chronic or severe it can lead to accelerated age-related cognitive decline (116) or even persistent cognitive impairment (117). Medial temporal lobe (MTL) structures appear particularly sensitive to systemic inflammation. This may reflect their higher BBB permeability (118) and pro-inflammatory cytokine receptor expression leading to heightened humoral interoceptive signaling (119, 120), or alternately their connectivity to insula (121) and consequent sensitivity to neural interoceptive signaling (115).

In rodents, peripheral inflammation induces IL-1 expression within the MTL (122) and replicates many of the direct actions of inflammatory cytokines on MTL-dependent memory including impaired spatial memory (3). In humans, naturalistic and experimental inflammatory challenges are associated with acute (reversible) impairment in spatial, verbal and nonverbal declarative memory (115, 123, 124). These effects are restricted to MTL-dependent memory i.e. they do not perturb procedural memory and appear to be mediated via actions of inflammation on MTL glucose metabolism (115). However, when inflammation is chronic it has been linked to reductions in hippocampal volume (125, 126). This has important implications for psychiatry, particularly the neuropathology of depression, which is associated with both raised inflammatory markers and reduced hippocampal volume (127, 128). Furthermore, MTL-dependent episodic memory impairment is one of the most commonly observed cognitive deficits in depression (129-131). Future studies will need to better understand the molecular mechanisms through which sustained interoceptive signaling of peripheral inflammation leads to persistent changes in MTL structure, determine whether modifiable factors can reverse this process, and clarify the significance of this link to the pathophysiology of inflammation-associated depression.

TREATMENT IMPLICATIONS

Above, we have highlighted the diverse interoceptive pathways recruited during the central signaling of inflammation and its subsequent impact on regional neuronal function and behavior. Identification of the molecular and cellular mechanisms that mediate these effects is revealing novel therapeutic targets and leading to a reappraisal of how some established therapies might exert therapeutic efficacy.

Perhaps the clearest example of a therapy directly targeting interoceptive mechanisms is vagal nerve stimulation (VNS), which exhibits potent anti-depressant properties (132). Though its mode of action is still only partially understood, it is now believed that actions on visceral afferent fibers at least partially underlie its clinical efficacy. However, VNS also modulates the efferent arm of the inflammatory reflex, inhibiting peripheral TNF, IL-1, and IL-6 production in humans (133). This anti-inflammatory action results in a reduction in circulating cytokines and consequently reduces signaling via humoral interoceptive pathways. Prolonged VNS also increases the firing rate of both serotonergic, and noradrenergic neurons in the brainstem that are each implicated in the pathophysiology of depression (134). It remains to be clarified how many of these effects are achieved through modulation of interoceptive signaling of inflammation.

Another strategy adopted in depression is the use of 'anti-cytokine' therapies to block cytokine signaling across interoceptive pathways. These agents (e.g. anti-TNF therapies) powerfully reduce circulating cytokine levels. Despite being unable to cross the BBB, they also reduce depressive symptoms suggesting an action through inhibition of interoceptive signaling (135, 136). Consistent with this, anti-depressant effects appear limited to individuals with raised inflammatory markers and by extension, interoceptive signaling of inflammation (135). Other approaches e.g. the use of non-steroidal anti-inflammatory drugs (NSAIDs) target specific interoceptive mechanisms. During systemic inflammation, cytokines

act on the brain endothelium to trigger release of lipophilic prostaglandins that readily diffuse across the BBB to exert central effect (35). By inhibiting prostaglandin production NSAIDs block this interoceptive-signaling pathway. In the context of acute inflammation they alleviate flu-like symptoms; meta-analysis also suggests efficacy in patients with depression (137), though this remains controversial with some studies even suggesting worsening of depressive symptoms (138). This will need careful evaluation in future larger scale clinical trials.

Another strategy is to target microglia, which appear central to transducing interoceptive signaling of peripheral inflammation into changes in neural function. One example of a microglial active agent is minocycline, a tetracycline antibiotic that readily crosses the BBB and inhibits microglial activation in rodents (77). Minocycline has demonstrated antidepressant properties in pre-clinical studies, in an open-label trial for bipolar depression (78) and in a recent randomized controlled trial of adjunctive treatment of MDD (79). It also has reported efficacy for negative symptoms in schizophrenia (80). However, minocycline has many additional actions that limit mechanistic interpretation of these studies (139). An alternative target is microglial P2X7 receptors that govern microglial IL-1 release and can modulate CNS chemokines, glutamate, and nitric oxide (140). In preclinical studies P2X7 knockout mice show a protective phenotype in models of depression. However, further human in vivo trials are needed to test its therapeutic effects in depression and characterize phenotypes that may be most conducive to this therapeutic approach.

SUMMARY

The immune system is a diffuse sensory 'organ' that uses parallel neural, humoral and cellular pathways to communicate peripheral immune signals to the brain. However, the immune system does not act in isolation. Top down influences from the brain can dampen

or even prime peripheral immune responses. In the latter case this appears to provide a form of innate immune memory for previous stress exposure, which then utilizes cellular interoceptive mechanisms to heightened behavioral responses in the face of subsequent stress. Though adaptive in the short term, when immune activation is prolonged or severe or occurs in specific neurodevelopmental contexts it can give rise to psychiatric disorders such as depression, schizophrenia, and ASD. Developing understanding of the complexity of these interacting communicatory pathways is rapidly forcing a broadening of how we conceptualize interoception. It is also motivating the development and repurposing of novel immunotherapeutic agents potentially heralding an exciting new era of immunotherapies for use in psychiatry.

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DISCLOSURES

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TABLE 1: Human imaging studies linking inflammation to regional changes in brain structure/function

| | Publications | Participants | Technique |
|--|--|--|--|
| Neural interoception: Insula | Rosenkranz 2005 (72) Harrison 2009 (19) Hannestad 2012 (18) Harrison 2015 (20) Harrison 2015 (20) Lekander 2016 (141) | 6 (WS) 16 (WS) 9 (WS) 20 (WS) 20 (WS) 48 (BS) | fMRI fMRI FDG PET FDG PET qMT rs-fMRI |
| Reward: Ventral Striatum | Eisenberger 2010 (73) Capuron 2012 (53) Haroon 2014 (54) Harrison 2016 (77) Felger 2016 (39) | 39 (BS) 28 (BS) 31 (BS) 24 (RM) 48 (correlation) | fMRI F-DOPA-PET MRS fMRI rs-fMRI |
| Memory: Medial temporal lobe | Marsland 2008 (126) Harrison 2014 (115) Raz 2014 (142) Satizabal 2012 (143) Baune 2012 (144) | 76 (correlation) 20 (RM) 80 (correlation) 1841 (correlation) 303 (correlation) | sMRI FDG-PET sMRI sMRI sMRI |
| Psychomotor slowing: Substantia nigra | Brydon 2008 (88) | 16 (RM) | fMRI |

Participants: Study design is reported as: WS – Within Subject, BS – Between Subject, Correlation – correlational analysis. Technique: fMRI (functional MRI), FDG PET Fluorodeoxyglucose PET, qMT (quantitative Magnetization Transfer MRI), rs-fMRI (resting state functional MRI), sMRI (structural MRI).

FIGURE LEGENDS

Figure 1: Peripheral Inflammation activates a neurally mediated interoceptive pathway

Convergent data from diverse imaging techniques show that peripheral inflammation activates a neurally mediated interoceptive pathway projecting to insula. A) Mild pro-inflammatory challenge using the Typhoid vaccine model increases BOLD signal within the human interoceptive brain regions including lateral thalamus (encompassing basal and posterior ventromedial nuclei (VMb and VMpo)) and cortical projections to dorsal mid/posterior and anterior insula within 3 hours of challenge (Modified from 19 with permission). B) LPS-induced peripheral inflammation increases Fluorodeoxyglucose (FDG) uptake with ventrolateral thalamus and posterior and anterior insula within 2 hours of inflammatory challenge (Modified from 18 with permission). C) Mild inflammation (induced using Typhoid vaccination) increases mid/posterior insula FDG-Glucose uptake (lower figure) and magnetization transfer from molecular-bound to free water (upper figure) within 4 hours of inflammatory challenge (Modified from 20 with permission).

Figure 2: ‘Circuit’ diagram illustrating visceral, humoral and cellular interoceptive signaling pathways and the major points of interaction

Figure 3: Role of humoral interoceptive pathways in anxiety and depressive-like behavior

A) During homeostatic conditions neuron-derived regulatory factors, such as CX3CL1 and TGF β maintain microglia in a ‘resting’ state. Low levels of effector monocytes circulate in the blood patrolling for pathogens or tissue damage and a small number of brain macrophages reside in the perivascular space to sample the brain microenvironment. B) During severe

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psychosocial stress microglia respond to damage-associated molecular patterns (DAMPs) and elevated ATP released from neurons to adopt an 'activated' phenotype. Simultaneous increase in sympathetic output results in an increase in circulating monocytes and consequently brain macrophages. These monocytes are believed to traffic to stress-associated brain regions and amplify pro-inflammatory responses through humoral interoceptive pathways involving vascular endothelial IL-1 receptor type-1 signaling. Modified from (145) with permission)

Figure1

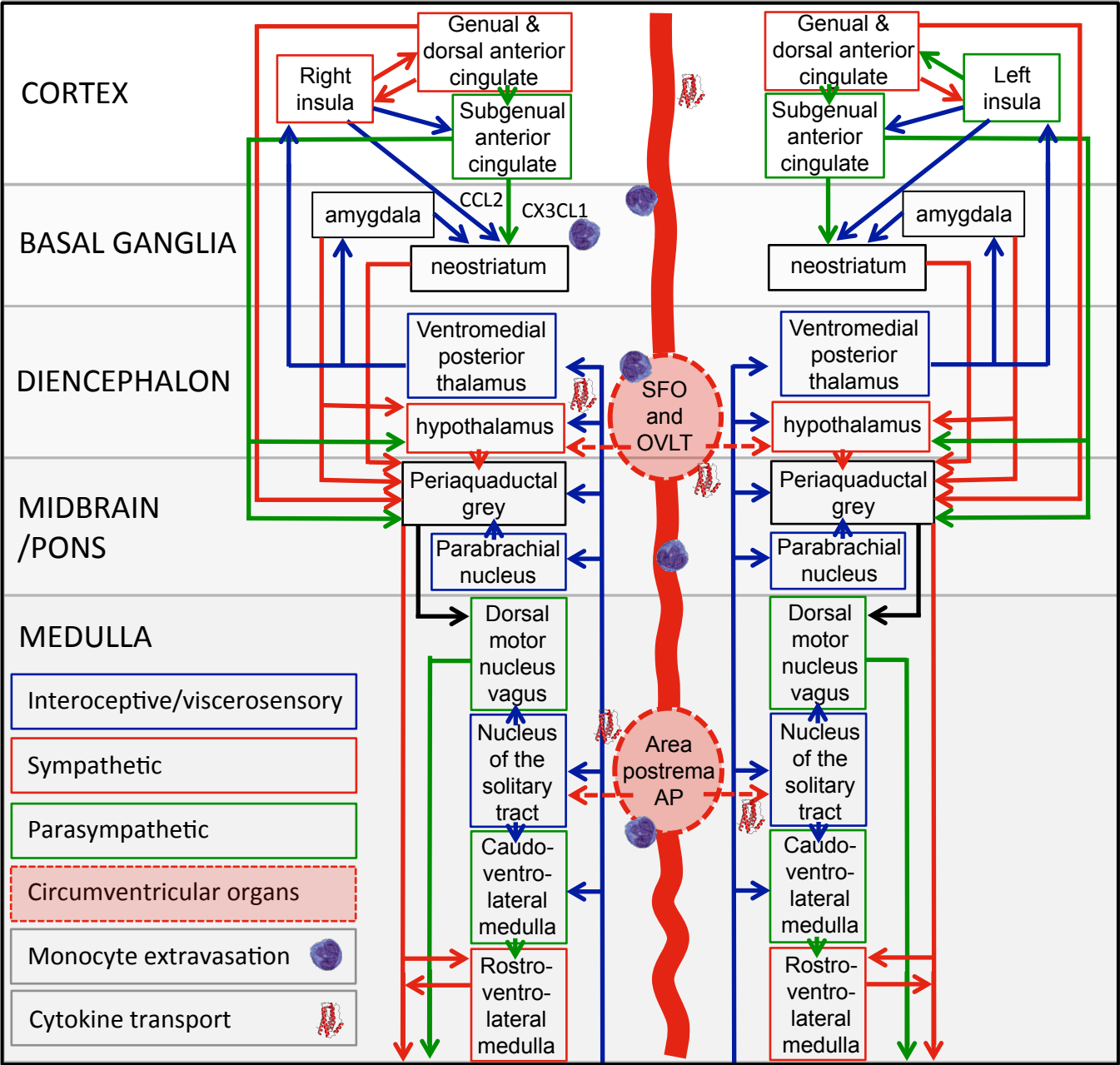


Figure2

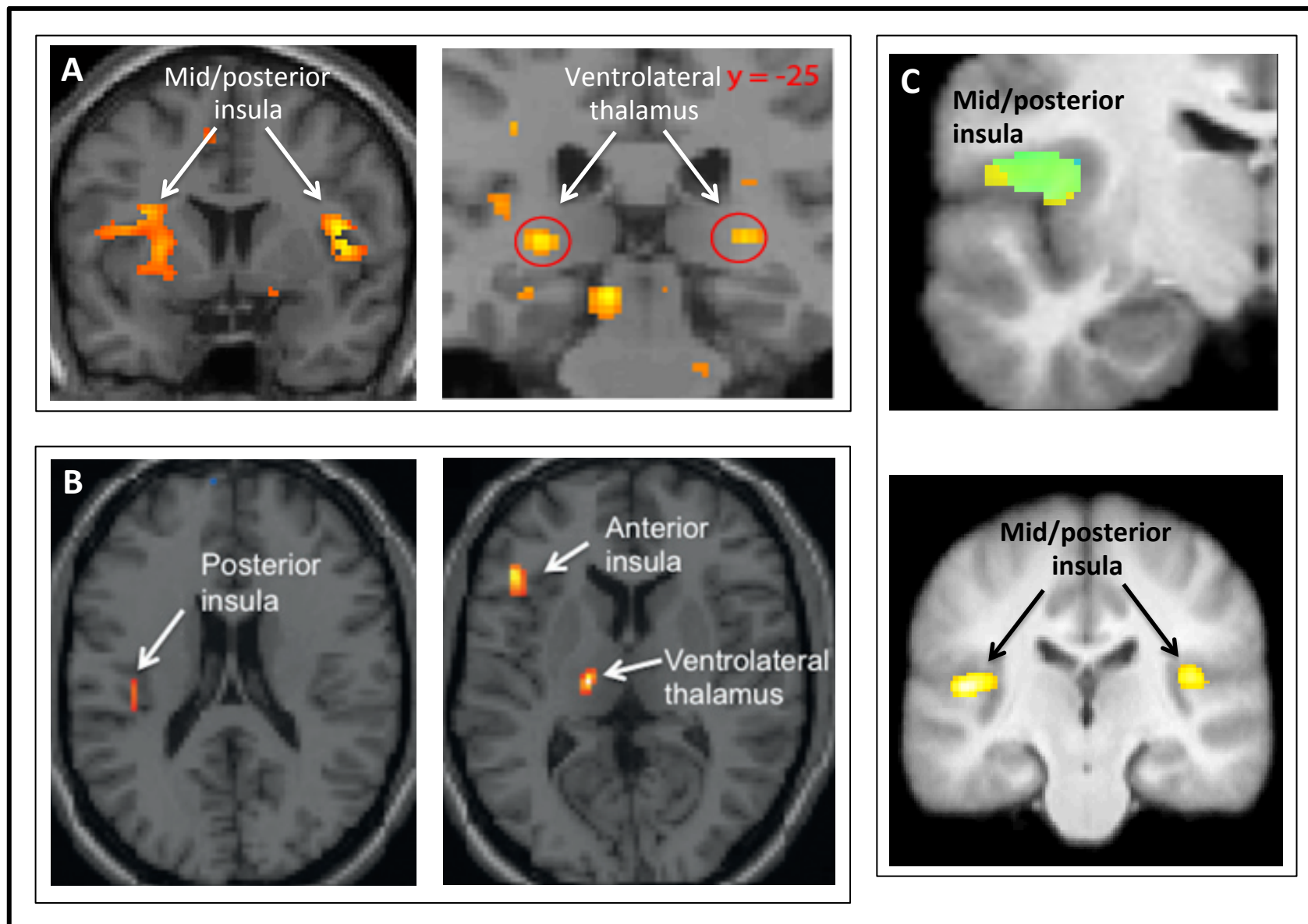


Figure3

